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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/859,722	05/17/2001	William Stuart Somers	W2025-700110 / AM100225	2770

76595 7590 08/25/2008

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ART UNIT	PAPER NUMBER
1656	

NOTIFICATION DATE	DELIVERY MODE
08/25/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	09/859,722	SOMERS ET AL.	
	Examiner	Art Unit	
	SUZANNE M. NOAKES	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 April 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *15,16,36-41,43-50 and 53-72* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *15,16,36-41,43-50 and 53-72* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

1. The response to the previous Office action and amendments to the claims filed 07 April 2008 are acknowledged. Applicants have added new claims 70-72 and canceled claims 42, 51 and 52. Thus, claims 15, 16, 36-41, 43-50 and 53-72 are pending and subject to examination.

Withdrawal of Rejections/Objections

2. Any rejection/objection recited in the previous Office action and not explicitly restated below is hereby withdrawn.

3. The rejections under 35 U.S.C. 112 1st paragraph, scope of enablement and written description, are withdrawn in-part with respect to claims 66-69 in view of Applicants arguments. The rejections are drawn to those claims which recite the use of P-selectin LE crystals, whereas claims 66-69 (and new claims 70-72) are directed to methods using structure coordinates only.

Maintained Rejections

Claim Rejections - 35 USC § 112 – 1st paragraph

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Scope of Enablement:

5. Claims 15, 16, 36-41, 43-50 and 53-65 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for identifying an agent that interacts with P-selectin LE by providing a crystal consisting of P-selectin LE selected from the group consisting of: a) a P-selectin LE crystal of a P-selectin EGF/lectin binding domain consisting of SEQ ID No: 6 and having space group $P2_1$ with unit cell parameters of a=81.0 Å, b= 60.8 Å, c=91.4Å and β=103.6°; b) a P-selectin LE co-crystal of a P-selectin EGF/lectin binding domain consisting of SEQ ID No: 6 complexed with SLe^x and having space group $P2_1$ with unit cell parameters of a=81.1 Å, b= 60.5 Å, c=91.4Å and β=103.3°; and c) a P-selectin LE co-crystal of a P-selectin EGF/lectin binding domain consisting of SEQ ID No: 8 complexed with PSGL-1 (SEQ ID No: 10) and having space group I222 with unit cell parameters of a=63.4 Å, b= 96.8 Å and c=187.3Å; determining the structural coordinates of said crystals and generating 3-D models therefrom of P-selectin LE having the structural coordinates of Figure 2, 3 or 5 ± 0.5-1.5 Å and employing said 3-D structure to design or select an agent that interact with said P-selectin LE, does not reasonably provide enablement for the method which uses any P-selectin LE crystal or those with conservative substitutions thereof, and which further can form in any of the 65 space groups with corresponding unit cell parameters. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The details of the rejection can be found in the previous Office action (15 June 2007), Section 5.

Written Description:

6. Claims 15, 16, 36-41, 43-50 and 53-65 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The claims are drawn to *in silico* methods of identifying agents that interact with a P-selectin lectin and EGF (LE) domains wherein said method provides a crystal comprising a P-selectin LE comprising SEQ ID Nos: 6, 8 or 9, or those with conservative substitutions thereof. Thus, the claims are intrinsically drawn to large number of species of P-selectin crystals containing a considerable number of different P-selectin proteins and thus the claims possess a large genus of widely variant crystals of both P-selecting proteins used to make the crystals. Also, as noted above, the crystal can have any ligand bound to the P-selectin LE. However, the specification only adequately describes three representative species in terms of both structure and function which belong to this genus.

The details of the rejection can be found in the previous Office action (15 June 2007), Section 6.

Claim Rejections - 35 USC § 103

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

8. Claims 66-69 and new claims 70-72 are rejected under 35 U.S.C. 103(a) as being unpatentable over Revelle et al. (JBC, 1996, 271(27):16160-16170 – cited on the IDS from 10 December 2001) in view of Morris et al. (J. of Computer-Aided Molecular Design. 1996. Vol. 10, pp. 293-304 – cited previously on PTO-892 of 7-3-06) in view of *In re Gulack* 217 USPQ 401 (Fed. Cir. 1983) and *In re Ngai* 70 USPQ2d 1862 (Fed. Cir. 2004). See MPEP §§ 2144 and 2144.04 regarding legal precedent as a source of rationale for rejection under 35 U.S.C. § 103.

The details of the rejection can be found in the previous Office action (15 June 2007), Sections 8 and 9.

New Rejections and Objections

Claim Objections

9. Claims 39, 63 and 66 is objected to because of the following minor grammatical errors:

A. In claim 39, 3rd line, P-selectin "LB" is recited rather than 'LE'.

B. In claim 63, 2nd line, “SEQ ill NO:” is recited rather than ‘SEQ ID NO:'.

C. In claim 66, after part (iii), "P-selecting" is recited rather than 'P-selectin'.

Appropriate corrections are required.

Claim Rejections - 35 USC § 112 – 1st paragraph

10. Claims 66-72 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to methods of identifying an agent that interacts with P-selectin LE by providing *relative structural coordinates* of a P-selectin LE which comprises SEQ ID Nos: 6, 8 or 9 wherein the relative structural coordinates are selected from Figures 2, 3 or 5 ± 0.5-1.5Å rmsd.

It is noted that Applicants specification on p. 15 defines the use of "structural coordinates" and their applicability to the instant application. It is clearly identified that structural coordinates can be obtained using NMR, homology modeling, x-ray crystallography etc. Furthermore, the structural coordinates of the instant invention of Figures 2-5 can be modified by mathematical manipulation and as such, the structural coordinates of the present invention are *relative*, "and are in no way specifically limited by the actual x, y, z, coordinates of Figures 2, 3, 4 and 5". (see p. 15, lines 7-19).

Thus, it is deemed that the claims encompass a wide and variable genus of distinct three-dimensional structural coordinates sets (e.g. species) which are not limited

to Figures 2- 5 by any means, wherein said Figures are the only four species described in the specification. These structural coordinates (Figs. 2- 5), however, are not considered to be representative species for the wide variation of structures found within the three-dimensional structure genus which includes variable structures derived from protein crystallography, NMR or homology model structures.

The MPEP states that the purpose of the written description requirement is to ensure that the inventor had possession, at the time the invention was made, of the specific subject matter claimed. The courts have stated:

> "To fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention." *Lockwood v. American Airlines, Inc.*, 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997); *In re Gostelli*, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) ("[T]he description must clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed."). Thus, an applicant complies with the written description requirement "by describing the invention, with all its claimed limitations, not that which makes it obvious," and by using "such descriptive means as words, structures, figures, diagrams, formulas, etc., that set forth the claimed invention." *Lockwood*, 107 F.3d at 1572, 41 USPQ2d at 1966." *Regents of the University of California v. Eli Lilly & Co.*, 43 USPQ2d 1398.

Further, for a broad generic claim, the specification must provide adequate written description to identify the genus of the claim. In *Regents of the University of California v. Eli Lilly & Co.* the court stated:

> "A written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." *Fiers*, 984 F.2d at 1171, 25 USPQ2d 1601; *In re Smythe*, 480 F.2d 1376, 1383, 178 USPQ 279, 284985 (CCPA 1973) ("In other cases, *particularly but not necessarily, chemical cases, where there is unpredictability in performance of certain species or subcombinations other than those specifically enumerated, one skilled in the art may be found not to have*

been placed in possession of a genus ...") *Regents of the University of California v. Eli Lilly & Co.*, 43 USPQ2d 1398.

In the instant case, as noted above, the specification makes clear that the "relative structure coordinates" are not meant to be limiting and can instead be considered non-limiting. Thus, while claim 66 recites Figures 2, 3 and 5, the term "relative structural coordinates" accompanying said Figures renders the claim broadly, but reasonably interpreted, as encompassing a large genus of structures encompassed within the claims. However, because there are only three structures of P-selecting LE disclosed in the instant specification which are representative of the entire broad and variant genus, this is deemed insufficient. The description requirement of the patent statue requires a description of an invention, not an indication of a result that one might achieve if one made that invention. See *In re Wilder*, 736, F.2d 1516, 1521, 222 USPQ 369, 372-73 (Fed. Cir. 1984) (affirming rejection because the specification does "little more than outlin[e] goals appellants hope the claimed invention achieves and the problems the invention will hopefully ameliorate."). Accordingly, it is deemed that the specification fails to provide adequate written description for the genus of the claims and does not reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the invention as claimed because the three species of P-selectin structures and one species of an E-selectin structure (Figure 3) are not deemed representative of the large and variable "relative three-dimensional" structure genus.

Response to Arguments

11. Applicant's arguments filed 07 April 2007 have been fully considered but they are not persuasive.

35 U.S.C. 112 – 1st Scope of Enablement:

12. The examiner has maintained the rejection of claims 15, 16, 36-41, 43-50 and 53-65 under the scope of enablement part of 35 U.S.C. 112 1st paragraph. The Examiner acknowledges that the withdrawal of this rejection with respect to claims 66-72 has been necessitated in-part by Applicants arguments (see above - Withdrawal of Rejections) that said rejection is not relevant to these particular claims which do not involve any protein crystals, just structure coordinates.

The Examiner acknowledges Applicants amendments to the claims to remove "an" from the independent claims 15 and 56 and also adding specific space groups $P2_1$ and I222, thus overcoming one aspect of the rejection. However, the remainder of the rejection is still relevant, namely and focusing on: the recitation of conservative substitutions, lack of unit cell parameters and the identifiable ligands which have been co-crystallized with the P-selectin.

Applicants traverse the remaining aspects of the rejection. In the first instance, it is stated (see Remarks, p. 13, 2nd full paragraph):

> "Applicants submit that once crystallization parameters are established and optimized (as it is the case in the instant application), one of ordinary skill in the art would have been able to generate de novo crystals of P-selectin LE in uncomplexed or complexed form within the space groups specified, without undue experimentation. This conclusion is consistent with the McPherson

reference cited by the Office…"

Applicants are relying upon the fact that they have determined three different crystal species for P-selectin LE in apo-form or with two different ligands (PGSL-1 and SLe^x) which form in space groups $P2_1$ or I222. It is asserted that because the present disclosure details the experimental conditions with the parameters that impact P-selectin LE crystal formation and optimization, that one skilled in the art could subsequently be able to produce other protein crystals in this space group with minimal effort and routine screening and optimization.

However, it is noted that this is not always the case. As outlined in the instant (and previous) rejection, undue experimentation would be expected in the instant case because even the smallest change in any parameter in crystallizing a protein can have enormous consequences. Also as noted previously, McPherson (Eur. J. Biochem. 1990, 189:1-23 – cited previously) has outlined 25 different parameters which do or could affect crystallization (see Table 2, p. 13). It is stated (p. 13, 2nd column, *Factors influencing protein crystal growth*):

> Table 2 lists physical, chemical and biological variables that may influence to a greater or lesser extent the crystallization of proteins. The difficulty in properly arriving at a just assignment of importance for each factor is substantial for several reasons. *Every protein is different in its properties and, surprisingly perhaps, this applies even to proteins that differ by no more than one or just a few amino acids*. There are even cases where the identical protein prepared by difference procedures or at different times may show significant variations. In addition, each factor may differ considerably in importance for individual proteins.

Thus, given the expectation in the art of how unpredictable even the slightest changes can have, those proteins with "conservative substitutions" may be incredibly difficult, if not impossible, to make.

In response to this, Applicants submit Navia et al. (JBC, 1992) and Sauer et al. (Protein Science, 1995) as Exhibits A and B and purport at the time the instant application was filed, that protein variants with known crystallization parameters were likely to readily crystallize with similar crystal structures as long as the variations introduced did not markedly affect intermolecular crystal contacts or amino acid residues important for protein stability (i.e., within the hydrophobic core). Furthermore it is surmised that even mutations that had an effect in altering protein stability were found to crystallize with similar crystallization parameters as the native protein, emphasizing that well-folded proteins can exhibit crystallization properties similar to the non-mutated counterparts. And thus, in view of the teachings in the specification describing successful crystallization conditions for at least three variants of P-selectin LE and E-selectin, one of ordinary skilled in the art would have been able to generate the conservatively substituted variant of P-selectin and produce crystals of these variants, without undue experimentation (see Remarks, p. 14 (bottom) to p. 15).

However, it is noted that the premise of the enablement requirement is predicated upon not imposing undue experimentation on one skilled in the art. However, in the instant situation, the scope of the claims exceed that which is sufficiently enabled because in the science of protein crystallography it can be of little use to describe to a skilled artisan a starting point (e.g. protein crystallization conditions

of wild-type protein) without precise directions of how to get to the end point (e.g. the exact protein crystallization conditions for mutant protein). In the instant case Applicants' assert that because they are in possession of crystals and crystallization conditions of P-selectin and three different conditions (e.g. three different crystals), that it is reasonable to conclude that any or all conservative substitutions will be enabled and one skilled in the art could readily crystallize said proteins. However, this is contrary to the teachings in the majority of the prior art. The teachings of McPherson are noted above and it is asserted that some proteins that differ by no more than a few amino acids may not crystallize, even if the native protein has been crystallized.

McPherson also goes on to teach:

> Because each protein is unique, there are few means available to predict in advance the specific values of a variable, or sets of conditions that might be most profitably explored. Finally, the various parameters under one's control are not independent of one another and their interrelations may be complex and difficult to discern. It is therefore, not easy to elaborate rational guidelines relating to physical factors or ingredients in the mother liquor that can increase the probability of success in crystallizing a particular protein. The specific component and condition must be carefully deduced and refined for each individual.

As noted above, it is well documented that protein crystallization is an inexact science at best and that more often than not, luck in obtaining crystals plays a role rather than any sound or specific science. This is emphasized by a matter-of-fact article by R. Cudney (The Rigaku Journal, 1999, Vol. 16 No. 1, pp. 1-7 – cited previously):

> "Well, sure a lot of it is well thought out, elegant science in protein crystallization, but lots of turn and burn crystallization stuff is dumb luck. How do we know this? We do not read about dumb luck. Well, maybe we do, but it has been disguised as science. However, obvious dumb luck is not something we like to publish. We might back up and wrap the dumb luck in an elegant idea, but I have not read a Material and Methods Method section yet referencing dumb luck as the ingredient in any crystallization trial. But dumb

> luck is something we hear about at poster sessions, coffee breaks, in the vendor booths at trade shows, and while we are waiting for crystals to grow. We all experience dumb luck, whether we want to admit it or not." (see p. 1, 2nd paragraph).

Cudney goes on to detail several different cases of just how dumb luck has played a critical part in his laboratories 'successes' in growing seven different protein crystals (see pp. 1-6). Furthermore, Drenth et al. (cited previously) also state this fact that luck often times is involved and in their case the only reason crystals were obtained was because the air-conditioning broke down over the weekend thus raising the temperature in the lab to exact point needed for crystal growth (see Drenth, "Principles of Protein X-Ray Crystallography", 2nd Edition, 1999 Springer-Verlag New York Inc., Chapter 1, p. 19, 4th paragraph, lines 1-2). These are just three of the many references the Examiner could use to exemplify the incredible unpredictability in the field of protein crystallography.

While Applicants have shown a few contrary examples of successful crystallization of altered proteins, the prior art recognizes the extreme unpredictability of this inexact science and thus there would be a considerable expectation of undue experimentation required which is significantly greater than routine screening in the art.

Thus, contrary to assertion by Applicants that a skilled artisan would expect that any of the changes encompassed by the claims and conservative substitutions to the P-selectin as compared to what Applicants actually did, would readily produce similar crystals is unfounded; it is rather asserted that a skilled artisan would see that there is expectation of an incredible amount of *de novo* experimentation that must be performed in order to try to produce crystals encompassed by the claims. Just because one

possesses the crystallization conditions of a native protein, does not mean that a mutant protein will readily crystallize in the same conditions, same space group, or even at all, as with everything in crystallography, it is a trial-and-error situation and the crystallographer can only cross their fingers and hope that it will work (see Cudney above).

If in a science it is routine to find unexpected results that hinge on unexplained phenomena, for example, the air conditioner breaking down in the laboratory where the crystallization experiments have been set-up, so that the resulting temperature in the lab is raised so as to unexpectedly, unpredictably and luckily be raised to just the right temperature to enable crystal growth (see Drenth et al., p 19, 4th paragraph, lines 1-2), or wherein crystals will grow only if the person setting up the crystallization experiments holds the test tube containing the protein in their hand, rather than placing said test-tube back on ice in between each individual experiment (see Cudney, see p. 2-3, especially, p.3 – cited previously), then this is not considered to be an exact science, rather it is sketchy, unreliable and an unpredictable science which will mandate undue experimentation given the scope of Applicants claims. As noted, it is a science riddled with unexplained phenomena, wherein changing the tiniest thing, e.g. conservative amino acid substitutions, may have enormous consequences. Furthermore, as noted by McPherson, changing even a few amino acids may have enormous consequences to successful crystallization.

Thus, when all relevant factors of In re Wands are considered in their totality, the breadth of the claims is deemed to exceed the enablement provided by the specification and the rejection is maintained.

Written Description:

The examiner has maintained the rejection of claims 15, 16, 36-41, 43-50 and 53-65 as lacking written description. The Examiner acknowledges that the withdrawal of this rejection with respect to claims 66-72 has been necessitated in-part by Applicants arguments (see above - Withdrawal of Rejections) and that said rejection is not relevant to these particular claims (e.g. claims 66-72) which do not involve any protein crystals, just structure coordinates.

Applicants arguments which traverse the remainder of this rejection can be distilled down to: "the breadth of the P-selectin LE genus specified by the method claims is circumscribed to the recited relative structural coordinates, which are obtained from the active site of the P-selectin crystals having space group $P2_1$ or I222 recited by the claims. Given the sequence identity and structural limitations encompassed by the methods claims as amended herein, the claims provide sufficient characteristics in common to define the genus of crystals recited by the claimed methods." (see Remarks, pp. 16 (last paragraph) to p. 17). That is, Applicants are asserting that the three species of protein crystals described in the specification, which are: a) an apo-P-selectin LE crystal consisting of SEQ ID No: 6 and having space group $P2_1$ with unit cell parameters of a=81.0 Å, b= 60.8 Å, c=91.4Å and β=103.6°; b) a P-selectin LE co-crystal of a P-

selectin of SEQ ID No: 6 complexed with SLe^x and having space group $P2_1$ with unit cell parameters of a=81.1 Å, b= 60.5 Å, c=91.4Å and β=103.3°; and c) a P-selectin LE co-crystal consisting of SEQ ID No: 8 complexed with PSGL-1 (SEQ ID No: 10) and having space group I222 with unit cell parameters of a=63.4 Å, b= 96.8 Å and c=187.3Å; are representative of all the crystal species encompassed within the genus of P-selectin crystals claimed, e.g. those having any conservative substitutions of any of SEQ ID NO: 6, 8 or 9 and with diverse and variable unit cell parameters.

However, the Examiner disagrees with these assertions and rather asserts that these three protein crystals are not representative of the diverse structures of P-selectin proteins of SEQ ID NO: 6, 8 and 9, which further have as many as one conservative substitution to 160 conservative substitutions (e.g. the entire protein) made therein. The number of polypeptides and thus crystals encompassed within this genus of polypeptides/crystals is enormous as is the basic polypeptide and overall structural variation. It is asserted that the three species described are not representative of the whole genus of polypeptides/crystals because the structural variation can be huge given the breadth of the claims. Since Applicants have provided only two species of proteins (e.g. SEQ ID NO: 6 and 8) used in crystallization of P-selectin LE which resulted in 3 crystal form species, it is deemed these are not representative of the wide variation within the genus.

35 U.S.C. 103(a):

The Examiner has maintained the rejection of claims 66-69 and added new claims 70-72 as being obvious over Revelle et al. (JBC, 1996, 271(27):16160-16170 –

cited on the IDS from 10 December 2001) in view of Morris et al. (J. of Computer-Aided Molecular Design. 1996. Vol. 10, pp. 293-304 – cited previously on PTO-892 of 7-3-06) in view of *In re Gulack* 217 USPQ 401 (Fed. Cir. 1983) and *In re Ngai* 70 USPQ2d 1862 (Fed. Cir. 2004).

Applicants traverse this rejection and state that Revelle et al. is no more than a review of the effects of various mutations to E- and P-selectins; there is no teaching of any three-dimensional structures at all. Morris et al. as the secondary reference fails because it does not make-up for the deficiency of teaching the requisite three-dimensional structures of P-selectin of Figures 2, 3 or 5 but merely is a review of the in silico software program AutoDock. (see Remarks, p. 18. 2nd to last paragraph). Thus, the premise of the rejection lies and hinges on the fact that Figures 2, 3 and 5 are not given any patentable weight as they are asserted to be non-functional descriptive material, which is an interpretation of *Gulack* and *Ngai*.

Specifically it is stated:

> Applicants submit that the structural coordinates of Figures 2, 3 and 5 evaluated by the claimed methods impart functionality by changing the processing steps of the computer program, changing the structural coordinates of the P- selectin LE binding site and the candidate agent, which ultimately imposes a change in the screening and/or design process that leads to obtaining an agent that interacts with P- selectin LE.
>
> When the candidate agent is positioned in the active site of P-selectin LE, the particular structural coordinates of the P-selectin LE site recited in the claims provide a specific spatial relationship and energy surface between the binding site and the candidate agent. During the docking process, the orientation of the candidate agent is constantly adjusted in the binding site by interactive real-time energy calculations between the binding site and the candidate agent. The energy calculations provide feedback to the docking program and dictate how the computer program functions to find an energetically favorable conformation of the candidate agent. If the interaction between the binding site and the candidate agent moves uphill in energy, this feedback will dictate the computer program to resist the motion. If the interaction between the binding site and the candidate

> agent is favorable, the feedback with dictate the computer program to encourage the motion (See N. Claude-Cohen et al. (1990) J. of Med. Chemistry 33(3):883-894, submitted herewith as Exhibit C). Thus, the structural coordinates of the P- selectin LE binding site recited in the claims dictate how the computer program functions.

However, these seem to establish a case that the structural coordinates are non-functional descriptive material rather than that Figures 2, 3 or 5 are actually functional because all of the manipulations are done by the computer program with little to no input by any one person or skilled artisan. The P-selectin LE three-dimensional coordinates are input into a computer program, specifically designed to use any or all three-dimensional structural coordinates and it is this program that iteratively finds the best fit of candidate small molecules by screening, for example, the hundreds of thousands of compounds listed in the Cambridge Structural Database (which would be considered an unbiased library, or alternatively, biased libraries – see p. 293, 1st column, 1st paragraph). However, there is no input from the user during the screening process which is happening *in silico* as there is no change to the programs design. It merely functions with any data which is input to said program. Thus, inputting any three-dimensional structure coordinates into a computer program which has specifically been designed to perform this function, does not make the data which is input into said program patentable nor does it make a method of inputting the data into a known program to perform its known and designed function patentable. It is noted that if the difference between the prior art and the claimed invention is limited to *descriptive* material stored on or employed by a machine, it must be determined whether the descriptive material is functional descriptive material or nonfunctional descriptive

material. If it is determined that the descriptive material is functional descriptive material and if this is a limitation in the claim, then said functional descriptive material must be considered and addressed in assessing patentability under 35 U.S.C. 103. Thus, a rejection of the claim as a whole under 35 U.S.C. 103 is inappropriate unless the functional descriptive material would have been suggested by the prior art. *In re Dembiczak*, 175 F.3d 994, 1000, 50 USPQ2d 1614, 1618 (Fed. Cir. 1999).

However, it is noted that *nonfunctional descriptive* material cannot render nonobvious an invention that would have otherwise been obvious. Cf. *In re Gulack*, 703 F.2d 1381, 1385, 217 USPQ 401, 404 (Fed. Cir. 1983) (when descriptive material is not functionally related to the substrate, the descriptive material will not distinguish the invention from the prior art in terms of patentability). This is especially true in the area of molecular drug design wherein Dean teaches (see Introduction, BioEssays, 1994, 16(9):683-687):

> "Drug design methods have made significant new advances over the last ten years, mainly in the areas of molecular modeling. In more recent times important developments in theory have led to a different type of modeling becoming possible, the so-called *de novo* or automated design algorithms. In this new method, the programs perform much of the chemist's thinking, in finding appropriately sized chemical groups to fit into a target site".

The examiner would further argue that it is not just in the *de novo* design that the programs perform much of the thinking but also when utilizing pre-existing libraries when screening using these same programs.

Accordingly, in the instant case, it would be obvious to input any three-dimensional structural data into a computer software program as taught by Morris et al. in order to carry out the software's intended use and function of identifying potential

ligands *in silico* by using any readily available data. Said three-dimensional data coordinates do not impart any functionality to the computer itself nor does it impart any functionality itself to the already preexisting computer software programs. It is analogous to asserting that inputting a set of data into an Excel Spreadsheet imparts functionality to the computer (the computer will run without both the Excel program or the data) that said Excel spreadsheet was loaded onto and/or that said data imparts functionality to the Excel spreadsheet itself. Rather the Excel spreadsheet will still operate in the manner it was designed by inputting any appropriate data set and the functionality of said Excel spreadsheet is not dependent upon any particular set of data. Thus, no one particular data set imparts functionality to the Excel spreadsheet. Likewise, no one particular three-dimensional coordinate data set imparts functionality to the programs taught by Morris et al. Using these programs in the manner for which they are designed would be obvious.

Thus, despite that fact that Revelle et al. does not teach Figures 2, 3 or 5, all of the arguments are drawn to the deficiency that Revelle et al. does not teach the requisite data and that Morris et al. does not remedy this deficiency. However, given that this data has been asserted to be non-functional descriptive material, it does not have to be taught in the prior art to establish a case of *prima facie* obviousness. Furthermore, it is noted that Morris et al. do cure some of the noted deficiencies of Revelle et al., namely they do teach a well known computer program designed specifically to perform the rationale drug design methods described in the specification. In fact, it is stated on p. 22-23 of the specification:

> "*Computer programs used to generate such three dimensional models and/or perform the necessary fitting analyses include, but are not limited to*: GRID (Oxford University, Oxford, UK), MCSS (Molecular Simulations, San Diego, CA), **AUTODOCK (Scripps Research Institute, La Jolla, CA), DOCK (University of California, San Francisco, CA)**, Flo99 (Thistlesoft, Morris Township, N J), Ludi (Molecular Simulations, San Diego, CA), QUANTA (Molecular Simulations, San Diego, CA), Insight (Molecular Simulations, San Diego, CA), SYBYL (TRIPOS, Inc., St. Louis. MO) and LEAPFROG (TRIPOS, Inc.,St. Louis, MO).
>
> The effect of such an agent identified by computer fitting analyses on P-selectin LE activity may be further evaluated by contacting the identified agent with P-selectin LE and measuring the effect of the agent on P-selecfin LE activity. Depending upon the action of the agent on the active site of P-selectin LE, the agent may act either as an inhibitor or activator of P-selecfin LE activity.

It is noted that AUTODOCK is the computer software program taught by Morris et al.

Thus, as asserted, these are well known computer software programs which have been created to perform rationale drug design with any set of three-dimensional coordinates. Thus, when utilized, for example with the three-dimensional coordinates of Figures 2, 3 or 5, a known predictable result will occur (namely finding good fitting candidate agents for a particular polypeptide) as this is what the computer program has been expressly designed to do.

As such the rejection of record is maintained and extended to the newly presented claims.

Conclusion

13. No claim is allowed; however, Applicants are encouraged to phone the Examiner for any clarification deemed necessary regarding the instant Office action and to discuss any potential allowable subject matter.

14. The new Written Description rejection for claims 66-72 was not necessitated by Applicants amendments and thus necessitates that the instant Office action is Non-Final.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to SUZANNE M. NOAKES whose telephone number is (571)272-2924. The examiner can normally be reached on 7.00 AM-3.30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr Bragdon can be reached on 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Suzanne M. Noakes/
Examiner, Art Unit 1656
18 August 2008